Effectiveness and Tolerability of Anticoagulants for Thromboprophylaxis after Major Joint Surgery: a Network Meta-Analysis

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Key Words
Anticoagulants • Thromboprophylaxis • Arthroplasty • Replacement • Meta-analysis

Abstract
Background/Aims Venous thromboembolism (VTE) is the most common complication after major joint surgery. VTE can easily develop into pulmonary embolism (PE), leading to cardiopulmonary dysfunction or sudden death. We aimed to comprehensively analyse the thromboprophylactic drugs that are used to prevent thrombosis and reduce bleeding risk.

Methods: We searched the PubMed, EMBASE, and Cochrane databases for randomized controlled trials that evaluated the use of thromboprophylaxis after major joint surgery. The major outcomes were the numbers of all-cause VTE and bleeding events, and the secondary outcomes were major VTE and major bleeding/clinically relevant non-major bleeding events. A random-effects network meta-analysis was used to assess the effectiveness and tolerability of each anticoagulant after major joint surgery. Results: We included 104 trials that assessed 110,643 patients in our meta-analysis. The cluster ranking of major outcomes indicated that FXI-ASO, ardeparin, aspirin, and apixaban were ideal for preventing all-cause VTE and avoiding all bleeding events. Nadroparin, recombinant hirudin, and rivaroxaban effectively inhibited VTE but were associated with a high risk of bleeding. For secondary outcomes, we found that betrixaban, dalteparin, warfarin, and eribaxaban were ideal for preventing major VTE and reducing major bleeding, while rivaroxaban effectively inhibited major VTE but was associated with a high risk of major/clinically relevant non-major bleeding. A sensitivity analysis showed that the effect of apixaban was more robust for major outcomes, while aspirin was more robust for preventing all-cause bleeding events. In secondary outcomes, the effect of warfarin was more robust, while apixaban was still considered an ideal treatment to inhibit major VTE and bleeding events. Conclusion: Our study indicates that FXI-ASO, ardeparin, aspirin, and apixaban are ideal for preventing all-cause VTE and reducing all bleeding events, among which apixaban is the most reliable. Betrixaban, dalteparin, warfarin, and eribaxaban are ideal for preventing major VTE and reducing major/clinically relevant non-major bleeding events, among which warfarin is the most reliable.
Introduction

Total knee/hip replacement, or arthroplasty, is the preferred method for treating end-stage joint disease [1, 2]. Venous thromboembolism (VTE) is the most common complication after surgical treatment [3, 4]. VTE comprises deep vein thrombosis (DVT) and pulmonary embolism (PE) and is the third leading cause of death by cardiovascular complications after myocardial infarction and stroke [5, 6]. In particular, after a major orthopaedic surgery, thrombosis is the most common cause of death, and it easily develops into PE, which can cause cardiopulmonary dysfunction or sudden death [7, 8].

The incidence of VTE includes three clinical elements: vascular endothelial injury, slow blood flow, and a hypercoagulable state [9, 10]. Patients who undergo major surgery with all of the above risk factors tend to develop DVT as a result of a variety of factors, including surgical injury and limb activity restriction. A previous study showed that in patients who underwent major hip or knee surgery without anticoagulation treatment, the incidence of DVT was 45%-84% [11]. As the population ages, there will be a corresponding increase in joint replacement surgeries, and the incidence of postoperative DVT is also likely to gradually increase [12].

Because DVT is a concealed condition that is difficult to clinically diagnose, high-risk patients need to actively take thromboprophylactics [13]. While the application of anticoagulants is an important routine prevention method, other strategies, such as avoiding prolonged bed rest, mechanical extrusion, and the use of compression stockings, are also recommended. A previous study recommended the use of thromboprophylactic therapy for 35 days after total hip arthroplasty (THA) and for more than 10 days after total knee arthroplasty (TKA) [14, 15].

A variety of anticoagulant drugs are available for clinical applications, including heparin derivatives, vitamin K antagonists, direct thrombin inhibitors, and direct factor Xa inhibitors. When new drugs are initially applied, researchers tend to pay more attention to their effects on the prevention of thrombus formation. However, an increasing number of studies have found that these drugs are associated with a higher incidence of bleeding [16, 17]. Therefore, we aimed to comprehensively analyse the thromboprophylactic drugs that are used to prevent thrombosis and reduce bleeding risk.

There is a long history of research regarding the use of anticoagulant drugs after major joint surgery, and a variety of results have been reported. Many systematic reviews and meta-analyses have been published in this area. Recently, an influential network meta-analysis aiming to compare any two direct factor Xa inhibitors reviewed the efficacy and safety of thromboprophylaxis following total hip or knee replacement [18]. The study included rivaroxaban, apixaban, betrixaban, darexaban, and edoxaban and indicated that the effects of these agents on total VTE risk ranked from low to high as follows: rivaroxaban, apixaban, edoxaban, enoxaparin, darexaban, and betrixaban. Their rankings for effects on major and clinically relevant non-major bleeding were as follows, from low to high: betrixaban, enoxaparin, darexaban, edoxaban, apixaban, and rivaroxaban.

Our analysis further expands on the included anticoagulants by including the results of previous studies. In addition, we increased the surgical category to include major hip or knee replacement, arthroplasty, and major surgery.

Materials and Methods

This meta-analysis was performed in accordance with the PRISMA (Preferred Reporting Items for Systematic Reviews) guidelines [19].

Data search strategy

We systematically searched the PubMed, EMBASE, and Cochrane Central Register of Controlled Trials databases using keywords that included "venous thromboembolism", "deep venous thrombosis", "postoperative venous thromboembolism", and "thromboprophylaxis". The search strategy included all clinical trials and observational studies published up to the date of analysis. The keywords were combined using the Boolean operators AND and OR to ensure comprehensive coverage of the literature. The search was limited to studies published in English to ensure comprehensibility and reliability of the results. The reference lists of included studies were also checked to identify additional relevant studies.
Data selection and extraction

The literature search and selection were independently performed by two authors, and all disagreements were resolved by discussion. A study was eligible for inclusion if it met the following criteria: 1. it included patients after total hip/knee replacement or arthroplasty or major joint surgery; 2. the patients received thromboprophylactic treatment after joint surgery; 3. the study had a randomized controlled design, and one group was treated with an anticoagulant drug, while another group was treated with a blank, placebo or alternate anticoagulant drug; and 4. one of the following outcomes was included in the study: the number of cases of all-cause VTE, major DVT/PE, all-cause bleeding events, and major bleeding/clinically relevant non-major bleeding events.

The exclusion criteria included the following: 1. the study included another type of surgery; 2. no patients were treated with anticoagulation agents (such as anesthetics); 3. the study did not include the desired results; 4. the study researched the dose-related effects of only one anticoagulant drug; and 5. the study was a mechanical stress treatment-related controlled trial. Additionally, reviews, conference presentations, letters, basic research articles, and editorials without sufficient data were excluded. Studies that failed to present original data were also eliminated.

We extracted the author, publication year, sample size, age, ratio of males to females, type of surgery, experimental intervention, control intervention, intervention time, subsequent treatment regimens, thrombus diagnosis, and follow-up period. We assessed the methodological quality of the included trials using a risk of bias approach according to the methods described by the Cochrane Collaboration [20]. In our analysis, the major effectiveness outcome was all-cause VTE, and the secondary effectiveness outcome was major DVT or PE. The major tolerance outcome was all-cause bleeding events, and the secondary outcomes were major bleeding/clinically relevant non-major bleeding events. For the efficacy outcome analysis, we used data from the intention-to-treat population, which comprised randomized patients who received a study agent. Because all the included studies had a randomized controlled trial design, our analysis did not classify the studies as low-risk and high-risk research. Most of the studies recommended or did not limit the application of compression stockings and mechanical extrusion, and we therefore treated mechanical intervention as a blank treatment. We also used the Grading of Recommendation Assessment, Development and Evaluation (GRADE) approach to assess the network meta-analysis quality, with four levels graded from high (best) to very low (worst). This method considered the quality of direct and indirect evidence as well as the quality of network evidence according to the inconsistency between direct and indirect evidence and the intransitivity among all related pieces of evidence. We performed “node splitting” to separate the indirect evidence from the direct evidence to inform these evaluations [21].

Statistical analysis

We performed a pairwise meta-analysis using a random-effects model. For dichotomous outcomes, odds ratios (ORs) with 95% confidence intervals (CIs) were calculated to determine the sizes of the effects. We also used a random-effects network meta-analysis for mixed multiple treatment comparisons because this approach fully preserves the within-trial randomized treatment comparisons in each trial [22]. Network plots were produced for each outcome, in which nodes are weighted according to the number of studies evaluating each treatment and edges according to the precision of the direct estimate for each pairwise comparison. When a treatment involved more arms, the node was larger, and when the comparison results were more accurate (small standard error), the edges were more weighted. The network analysis adopted a frequentist framework, and a contrast-based model was used to evaluate multi-arm trials. We used a multivariate random-effects meta-regression to pool data with proportional variance-covariance matrix, and a restricted maximum-likelihood method was used to assess model fit. Consistency within every closed triangle or quadratic loop was investigated using a loop-specific approach to evaluate the coherency between direct and indirect comparisons. During analysis, inconsistency factors (IFs) and their 95% CIs were used to determine their compatibility with zero [23].
To rank the treatments for each outcome, we used surface under the cumulative ranking (SUCRA) probabilities [24, 25]. The effectiveness and tolerability of each treatment are displayed as cluster-ranking plots. We assessed the sensitivity of results for the primary outcome by analysing only studies considered to be at low risk of bias. To address global inconsistency from all possible sources, we used a design-by-treatment interaction model when adjusting results for entire publication bias [26]. Comparison-adjusted funnel plots were used to determine whether small-study effects were present in our analysis [27].

**Results**

**Literature search**

In our study, 890 articles were identified after duplicates were removed. A total of 757 of these articles were excluded after the titles and abstracts were screened. The full text of the remaining 133 articles was assessed, and the following studies were removed: secondary research studies (8), mechanical treatment-related studies (8), studies that included other types of surgery (4), studies of anaesthetics and other drugs (3), studies that evaluated the duration of treatment (2), studies with undesired results (1), duplicate publications (1), studies without a randomized, controlled design (1), and studies that compared preoperative and postoperative drug treatments (1). Finally, 108 treatment comparisons that assessed 110,643 patients from 104 trials were collected in our systematic review (Fig. 1, Table 1) [28-135].

**Study characteristics**

The age range of the included patients was 30-80 years. Eight of these studies failed to clearly define the ages of the included patients, and three of the studies included patients who were more than 40 years old. In this type of surgery, most of the included studies included patients with knee or hip replacement or arthroplasty, and thirteen trials included patients with major joint surgery, such as hip or knee fracture (Table 1).

Thirty drugs were included in our analysis. They included vitamin K antagonists (acenocoumarol and warfarin), direct factor Xa inhibitors (apixaban, betrixaban, darexaban, edoxa-
One study was not included in the meta-analysis because two of the drugs researched in the study clearly did not overlap with other drugs. The drugs included in this study were acenocoumarol and reviparin [88]. Enoxaparin was the most frequently investigated intervention. All trials were found to have a low risk of bias for randomization, 10-20% for concealment of allocation, 58% for blinding of patients, and 73% for blinding of therapists. The included studies were all randomized controlled trials, and their overall quality was therefore ideal. All the trials clearly showed a benefit for the use of anticoagulants for thromboprophylaxis after major joint surgery.
als were randomly grouped, and only 2% of trials did not mention the means of random sequence generation. Additionally, 11% of trials did not explicitly mention allocation concealment. Therefore, randomization was completely reliable. In addition, 4% of trials did not explicitly define the reasons for the loss of participants. However, for application of blinding method, 44% of trials did not set blinding of participants and personnel, and 28% of trials did not set blinding for outcome assessments. Therefore, the most important bias was the influence of blinding methods on the results and the influence of subjective assessment bias factors.

In the results of these trials, the diagnosis of thrombus was generally based on venography, colour duplex Doppler, or other relatively objective methods if the assessor could be completely concealed; thus, the impact of low assessment blinding quality on the results was small. However, it still was not possible to exclude the influence of psychological suggestion of the participants and the investigator on the assessor. The judgement of bleeding results is often subjective, particularly if blinding methods are not well designed; therefore, this subjectivity would have a certain impact on the results.
Results of network meta-analysis

In the network meta-analysis, eligible comparisons of all-cause VTE outcomes are presented (Fig. 2), which show the predominantly pairwise comparisons of different anticoagulants used for thromboprophylaxis after major joint surgery. Treatments in the network that are not well connected should be interpreted with caution. Moreover, probabilities of which treatment is the best can be fragile when the network is sparse. We removed one study because no other interventions were associated with its interventions. Thus, 103 studies and 107 comparisons were included for the VTE results (Table 2). An inconsistency plot was produced to assume the loop-specific heterogeneity estimate; it found 23 triangular loops and 17 quadratic loops. Although there was no significant difference between direct and indirect comparisons, we found that there was a relatively large difference between direct and indirect comparisons related to placebo and blank interventions. These inconsistencies may have resulted from differences in the methods used to define thrombosis. We therefore used an inconsistency model to research pairwise comparisons, and the forest plot showed that enoxaparin was more advantageous than dextran (logOR, 1.39; 95% CI, 0.74-2.04; p<0.001), and nadroparin was superior to blank treatment (logOR, 1.09; 95% CI, 0.66-1.52; p<0.001). Other results showed no significant differences between anticoagulants, and only one study was included in that analysis [Data not shown]. It is notable that it may be improper to include data contained in multi-arm studies in a pairwise comparison analysis. Furthermore, we ranked the comparative effects of all anticoagulants in all VTE with SUCRA probabilities (%). The results indicated that rivaroxaban (88.4%), recombinant hirudin (85.6%), and ardeparin (82.7%) were most likely to reduce thrombosis after major joint surgery. These agents were followed by nadroparin (81.0%) and TB402 (76.9%). The comparison-adjusted funnel plot used to assess publication bias and to determine the presence of small-study effects did not suggest that there was any publication bias. However, the global inconsistency analysis showed that there was significant inconsistency among the studies (p = 0.0068).

Eligible comparisons of major VTE outcomes are presented in Fig. 3. The exp(\text{IF}) of the inconsistency plot that included 10 triangular loops and 3 quadratic loops showed that there was no significant difference among the studies. Therefore, we used a consistency model to research pairwise comparisons, and there were no observable low-heterogeneity differences among the comparisons. The comparative effects of all treatments and their SUCRA probabilities revealed that eribaxaban (85.9%), rivaroxaban (80.5%), and warfarin (71.9%) were most likely to reduce the risk of major thrombosis after major joint surgery, followed...
by apixaban (71.5%). The comparison-adjusted funnel plot did not reveal any publication bias, and the global inconsistency plot also showed that there was no significant difference ($p = 0.7907$).

The network plot for all-cause bleeding outcomes is shown in Fig. 4. The inconsistency plot included 15 triangular loops and 16 quadratic loops shows an exp(IF) with 4 loops larger than zero. Significant inconsistencies were found in the loops of ardeparin-blank-heparin-placebo ($p = 0.003$), aspirin-blank-heparin-placebo ($p = 0.01$), fondaparinux-heparin-placebo-warfarin ($p = 0.016$), and enoxaparin-heparin-placebo ($p = 0.038$) [Data not shown]. The consistency model was used to research pairwise comparisons, and no observable differences were found among the comparisons. The SUCRA probabilities showed that sudoxicam (92.2%), FXI-ASO (89.4%), and betrixaban (88.3%) were likely to be associated with the lowest risk of all-cause bleeding after major joint surgery. Additionally, there was no publication bias in the comparison-adjusted funnel plot. The global inconsistency showed no significant difference ($p = 0.2292$).

The network plot for major bleeding outcomes is shown in Fig. 5. ENO included the three most frequently researched treatments. The inconsistency plot including four triangular loops and six quadratic loops showed that there were no significant differences among the loops. The consistency model was used to research pairwise comparisons, and there were no observable differences in low heterogeneity among the comparisons. The SUCRA probability scores showed that betrixaban (86.9%), dalteparin (74.6%), and warfarin (66.1%) were associated with the lowest risk of major bleeding/non-major clinically relevant bleeding events. Additionally, there was no clear publication bias in the comparison-adjusted funnel plot, and there was no significant difference in global inconsistency ($p = 0.184$).
After we performed a comprehensive analysis of all-cause VTE and all bleeding events, the cluster ranking showed that FXI-ASO, ardeparin, aspirin, and apixaban were ideal for preventing all-cause VTE and avoiding all bleeding events. Nadroparin, recombinant hirudin, and rivaroxaban all effectively inhibited VTE but were associated with a high risk of bleeding events (Fig. 6). The cluster-ranking analysis of major VTE and major/clinically relevant non-major bleeding events showed that betrixaban, dalteparin, warfarin, and eribaxaban were ideal for preventing major VTE and reducing major bleeding events. Rivaroxaban effectively
inhibited major VTE but was associated with a high risk of major/clinically relevant non-major bleeding events (Fig. 7).

Quality of evidence and sensitivity analysis

We simplified the results of all the comparisons in the GRADE assessment and only listed treatments related to the final conclusion and its direct comparisons (Table 3). For all-VTE outcomes, apixaban had five direct comparisons with moderate and high quality. Although the quality level of aspirin in the network comparisons was generally low, the seventeen related direct comparisons increased the robustness of the results. Ardeparin had only two comparisons with moderate and low levels, and FXI-ASO had only one low-quality comparison. Thus, the results of these two treatments lacked robustness. In addition, there was incoherence between the direct and indirect comparisons of apixaban versus enoxaparin, ardeparin versus blank, ardeparin versus placebo, and aspirin versus placebo. For the all-cause bleeding outcome, apixaban had five direct comparisons with a high level of quality, and aspirin had ten direct comparisons with a generally moderate level. The results of ardeparin and FXI-ASO still lacked robustness.

For the major VTE outcome, warfarin had six direct comparisons with moderate and low quality; betrixaban, dalteparin, and eribaxaban all included only one direct comparison without robustness. For the major bleeding outcome, dalteparin had seven comparisons with a moderate-high level of quality; warfarin had four comparisons of a low-moderate level of quality. The results of betrixaban and eribaxaban were still not robust because of fewer comparisons. Additionally, for major VTE and bleeding outcomes, most included trials contained small sample sizes and zero-event results, which reduced the quality of evidence because of imprecision.
In the sensitivity analysis, we removed the relatively low-design-quality trials. For the all-cause VTE outcome, fondaparinux (SUCRA: 67% to 93.9%), rivaroxaban (SUCRA: 88.4% to 93%), edoxaban (SUCRA: 69.9% to 92.8%) were generally best. In conclusion-relative treatment, apixaban (SUCRA: 66.7%-82.8%) was still ideal, while aspirin (SUCRA: 52.8% to 26.1%), ardeparin (SUCRA: 82.7% to 23.2%), and FXI-ASO (miss) were less dominant. For the all-cause bleeding outcome, betrixaban (SUCRA: 88.3% to 52.5%), aspirin (SUCRA: 73.6% to 82.7%), and warfarin (SUCRA: 62.2% to 78.9%) were best. In key treatment, apixaban (SUCRA: 62.7% to 62.2%), aspirin (SUCRA: 73.6% to 82.7%), and ardeparin (SUCRA: 65.4% to 56.6%) were best. Combined with the GRADE results, apixaban and aspirin were relatively robust. Further, when only considering well-designed trials, the result of apixaban was more robust.

Table 3. Summary comparisons of the effect size and quality of major outcomes. Abbreviations: CIs: confidence intervals; LogOR: logarithm odds ratios; NA: not available. *: Study limitation; †: Indirectness; ‡: Imprecision; §: Incoherence

<table>
<thead>
<tr>
<th>Outcomes/Interventions</th>
<th>No. of studies</th>
<th>Direct comparisons (LogOR [95%CI])</th>
<th>Quality</th>
<th>Indirect comparisons (LogOR [95%CI])</th>
<th>Quality</th>
<th>Network comparisons (LogOR [95%CI])</th>
<th>Quality</th>
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<td>All-cause VTE</td>
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<td>Apixaban vs.</td>
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<td>Enoxaparin</td>
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<td>0.63 (-1.18, 2.45)</td>
<td>Moderate</td>
<td>-0.05 (0.89, 0.18)</td>
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<td>Warfarin vs.</td>
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<td>High</td>
<td>-1.69 (-2.20, 1.17)</td>
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<td>1.21 (-2.06, 0.36)</td>
<td>High</td>
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<td>Low‡</td>
<td>-0.97 (1.66, 0.27)</td>
<td>Moderate</td>
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<td>Placebo</td>
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<td>Low‡</td>
<td>-0.71 (1.44, 0.02)</td>
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<td>-0.01 (1.43, 0.30)</td>
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<td>0.00 (0.31, 0.15)</td>
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<td>-0.05 (0.49, 0.30)</td>
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<td>Low‡</td>
<td>-1.07 (1.74, 0.40)</td>
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<td>1.28 (-2.22, 0.93)</td>
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<td>-0.01 (1.43, 0.30)</td>
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<td>-0.02 (0.06, 0.70)</td>
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<td>-0.16 (1.85, 1.50)</td>
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<td>-1.30 (1.34, 1.40)</td>
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<td>-1.59 (1.37, 1.08)</td>
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<td>0.47 (-2.22, 1.29)</td>
<td>Moderate</td>
<td>-0.13 (0.07, 0.81)</td>
<td>High</td>
</tr>
<tr>
<td>Rivaroxaban vs.</td>
<td></td>
<td></td>
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<tr>
<td>Blank</td>
<td>1</td>
<td>0.51 (0.19, 0.83)</td>
<td>Moderate</td>
<td>0.71 (1.00, 0.65)</td>
<td>Moderate</td>
<td>0.14 (-0.60, 0.84)</td>
<td>Moderate</td>
</tr>
<tr>
<td>Dabigatran vs.</td>
<td></td>
<td>0.87 (0.47, 1.27)</td>
<td>Low‡</td>
<td>0.98 (0.47, 0.87)</td>
<td>Low‡</td>
<td>0.86 (0.31, 0.80)</td>
<td>Low‡</td>
</tr>
<tr>
<td>Rivaroxaban vs.</td>
<td></td>
<td>0.58 (0.47, 0.77)</td>
<td>Moderate</td>
<td>0.71 (1.00, 0.65)</td>
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<td>0.14 (-0.60, 0.84)</td>
<td>Moderate</td>
</tr>
<tr>
<td>Trifuxid vs.</td>
<td></td>
<td>0.92 (0.39, 1.47)</td>
<td>Moderate</td>
<td>0.34 (0.67, 1.75)</td>
<td>Moderate</td>
<td>0.56 (-3.01, 2.50)</td>
<td>Moderate</td>
</tr>
<tr>
<td>Warfarin vs.</td>
<td>1</td>
<td>0.04 (-2.84, 2.77)</td>
<td>Moderate</td>
<td>0.10 (0.05, 0.24)</td>
<td>High</td>
<td>-0.19 (0.64, 0.25)</td>
<td>High</td>
</tr>
<tr>
<td>FXI-ASO vs.</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Enoxaparin</td>
<td>1</td>
<td>1.17 (-2.23, 0.11)</td>
<td>Moderate</td>
<td>-0.10 (1.25, 1.01)</td>
<td>Low</td>
<td></td>
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</table>
For the major VTE outcome, rivaroxaban (SUCRA: 80.5% to 85.8%), apixaban (SUCRA: 71.5% to 73.5%), and warfarin (SUCRA: 71.9% to 70.8%) were generally best after removing low-quality studies. In key treatment, only warfarin had ideal results; other treatments were missing. For the major bleeding outcome, dalteparin (SUCRA: 74.6% to 81.6%), warfarin (SUCRA: 66.1% to 76.7%), and semuloparin (SUCRA: 65.8% to 72.7%) were the best treatments. In conclusion-related treatment, dalteparin, warfarin, and betrixaban (SUCRA: 86.9% to 56.8%) were still ideal; the result of eribaxaban was missing. Thus, in terms of secondary outcomes, warfarin had a robust effect, and apixaban still showed advantages in inhibiting major VTE and bleeding.

Discussion

In this study, we performed a network meta-analysis to analyse VTE and bleeding events in patients who underwent major joint surgery and were subsequently treated with thromboprophylactics. We included several types of anticoagulant in the analysis, including vitamin K antagonists, direct factor Xa inhibitors, factor XI antisense oligonucleotides, factor VIII inhibitors, direct thrombin inhibitors, non-steroidal anti-inflammatory agents, heparin and its derivatives, and platelet aggregation inhibitors. The results showed that FXI-ASO, ardeparin, aspirin, and apixaban were ideal for preventing all-cause VTE and reducing all bleeding events, while betrixaban, dalteparin, warfarin, and eribaxaban were ideal for preventing major VTE and reducing major/clinically relevant non-major bleeding events.

All-cause VTE events that have been described in clinical records typically include asymptomatic DVT, objective symptomatic VTE, and fatal PE, and the diagnostic methods used to evaluate these conditions have included venography (phlebography), ultrasonography, and an objective review of records [136]. The bleeding events that occur after anticoagulant treatment typically include clinically relevant bleeding (major or clinically non-major bleeding) and minor bleeding. Major bleeding was defined as a decrease in haemoglobin of 2 g per decilitre or necessitating transfusion of 2 or more units of blood [137], and clinically relevant non-major bleeding included non-major bleeding that required intervention or consultation with a physician and had clinical consequences [29]. Minor bleeding included haemorrhagic wound complications or other bleeding-related adverse events [138]. However, there may be slight differences among the assessors for VTE and bleeding judgement, especially in non-major events.

The loop-specific inconsistency analysis and GRADE assessment revealed some differences between direct and indirect comparisons. The cause of these inconsistencies may include differences in adjuvant therapy or physiotherapy, especially in blank and placebo intervention arms. In these empty intervention arms, other adjuvant therapy would be used to prevent thrombosis. The decision whether to undergo physiotherapy was due to the daily activity of patients. In addition, the zero-event trials may have made the direct and indirect comparisons less robust. In the comprehensive analysis, the effectiveness of apixaban was ideal and robust. Apixaban is a direct inhibitor of factor Xa that can directly combine with factor Xa to prevent coagulation cascades and is therefore widely applied in the clinical setting [139]. This mechanism of this anticoagulant may play a significant role in thromboprophylaxis after major joint surgery.

The sensitivity analysis revealed that aspirin was not ideal in preventing thrombosis, but it still had high tolerability to inhibit bleeding. We also found that five of twenty-five patients developed VTE in an arm that combined the use of heparin and aspirin and even applied compression treatment at the same time [111]. This finding suggests the combination of heparin and aspirin has negative synergistic effects for thromboprophylaxis.

In the global inconsistency assessment, we found the all-VTE outcome had complete inconsistency. It was notable that improvements in surgical technology and perioperative nursing could reduce thrombosis and bleeding events. Therefore, in theory, if more of these
trials are conducted, a smaller number of patients should experience thrombosis and bleeding. Major VTE was usually considered as a secondary outcome in the included studies. These cases included proximal DVT, non-fatal PE or deaths associated with VTE during follow-up. However, major bleeding events were usually treated as a major safety outcome in these studies. Our results indicated that betrixaban, dalteparin, apixaban, warfarin, and eribaxaban were ideal for preventing major VTE and reducing the risk of major bleeding. Rivaroxaban was effective at preventing thrombosis but was more likely to cause major bleeding events. It is interesting that betrixaban and eribaxaban, which are direct factor Xa inhibitors, were not ideal for preventing all-cause thrombosis or bleeding but provided advantages when treating major thrombosis and bleeding events. These drugs were potent, orally active and highly selective for factor Xa, and they were selected from a group of similar compounds because of their low affinity for the human ether-à-go-go-related gene (hERG) and showed favourable effectiveness for preventing PE in particular [140]. The U.S. Food and Drug Administration has granted a Fast Track designation to betrixaban for the extended-duration prevention of VTE in acutely ill patients. In this study, dalteparin and warfarin, a heparin derivative and vitamin K antagonist, respectively, were ideal for inhibiting major thrombosis and bleeding events. The effect of rivaroxaban was similar to the above all-cause results, which showed that this drug was effective at preventing major thrombosis but was associated with a high risk of major bleeding events.

Research aimed at preventing thrombosis after joint surgery is generally focused on the use of various types of anticoagulants. Therefore, a network meta-analysis could help us to obtain a more comprehensive understanding of the effectiveness of these drugs and patient tolerability in addition to allowing us to perform indirect comparisons. A previous network meta-analysis of direct factor X inhibitors described results that were similar to ours with regard for the ranking of drugs according to total VTE risk. These rankings were as follows, from high to low: rivaroxaban, apixaban, edoxaban, enoxaparin, darexaban, and betrixaban. The rankings for the ability to reduce major and clinically relevant non-major bleeding were as follows, from low to high: betrixaban, enoxaparin, darexaban, edoxaban, apixaban, and rivaroxaban. Our research also included other types of anticoagulants in addition to direct factor X inhibitors, such as factor XI antisense oligonucleotides, factor VIII inhibitors, direct thrombin inhibitors, non-steroidal anti-inflammatory agents and vitamin K antagonists. We comprehensively analysed all-cause thrombosis/bleeding events and major thrombosis/bleeding events to provide a valuable reference for clinical applications. However, as some anticoagulants included in our work are under development, those findings are of limited value for clinicians. Most importantly, surgical techniques and perioperative nursing have greatly evolved from the time of the first studies included in our work until now, such that the impact of such improvements on bleeding events and possibly on VTE events is potentially important.

There are several limitations to our study. First, our analysis was performed at the study level but not at the individual level. Second, there is unexplained heterogeneity in our analysis. This may result from differences in daily drug doses, application times, mechanical treatment effects, follow-up times, or thrombosis/bleeding event-related criteria because this field has gradually matured in recent years. Third, our study did not evaluate the use of haemoglobin, blood transfusion amounts, or blood drainage as assessment indexes in the analysis of results.

**Conclusion**

In conclusion, our study indicates that FXI-ASO, ardeparin, aspirin, and apixaban are ideal for preventing all-cause VTE and reducing all bleeding events, among which apixaban is the most reliable. Betrixaban, dalteparin, warfarin, and eribaxaban are ideal for preventing major VTE and reducing major/clinically relevant non-major bleeding events, among which...
warfarin is the most reliable. Overall, the results of apixaban for thromboprophylaxis after major joint surgery are particularly encouraging.

Disclosure Statement

The authors declare no conflict of interest.

References


